Paper No. 58

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte MICHAEL DORSCHUB, PAUL HABERMANN, GERHARD SEIPKE and EUGEN UHLMANN

Appeal No. 2001-1586
Application No. 08/402,394

ON BRIEF

Before WILLIAM F. SMITH, SCHEINER and ADAMS, Administrative Patent Judges.

WILLIAM F. SMITH, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from an examiner's final rejection of claims 21 through 23, 25 through 27 and 31. Subsequently, claims 33 through 42 were added. Thus, 21 through 23, 25 through 27, 31 and 33 through 42 are before us for review.

Claim 33 and 42 are representative of the subject matter on appeal and reads as follows:[1]

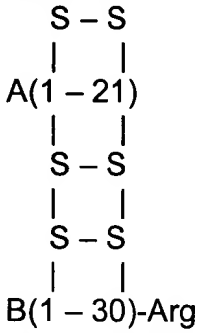
33. A compound of the formula I

B(1-30)-Arg-A(1-21)

(I)

wherein A(1-21) and B(1-30) denote the A and B chains of human insulin.

42. A method for the preparation of a mono-Arg-insulin compound of the formula II



(II)

in which A(1-21) and B(1-30) denote the A and B chains of human insulin and the –S-S-bridges are positioned as in insulin, which comprises:

(a) expressing a DNA sequence encoding a mini-proinsulin compound of the formula:

B(1-30)-Arg-A(1-31)

in a yeast; and

(b) cleaving said mini-proinsulin compound with trypsin.

The references relied upon by the examiner are:

Mai et al. (Mai)	5,087,564	Feb. 11, 1992
Markussen et al. (Markussen '212)	4,916,212	Apr. 10, 1990
Grau (Grau '684)	4,801,684	Jan. 31, 1989
Grau (Grau '332)	4,639,332	Jan 27, 1987

[1] We note that claim 42(a) requires the use of the compound B(1-30)-Arg-A(1-31) instead of B(1-30)-Arg-A(1-21). We view "A(1-31)" in the claim to be a typographical error as all references to this compound in the original disclosure of this application state that the A chain is depicted as "A(1-21)." Claim 21 also contains this apparent error. Our consideration of the issues raised in this appeal has been based upon claim 42(a) requiring the use of the compound B(1-30)-Arg-A(1-21). Note counsel's statement at page 8 of the Appeal Brief "the common subject matter to every pending claim is the compound of formula B(1-30)-Arg-A(1-21)."

Markussen et al. (Markussen EPO)	EPO 163,529	Dec. 4, 1985
Goeddel et al. (Goeddel)[2]	EPO 0,05,5945	Jul. 14, 1982

A reference of record discussed by this merits panel is:

Thim et al. (Thim)	EPO 0,195,691	Sep. 24, 1986

The claims stand rejected as follows:

Claims 21 and 33 through 36 under 35 U.S.C. § 103(a). The examiner relies upon Markussen '212 or Markussen EPO, Godeddel, Grau '684 and Grau '332 as evidence of obviousness,

Claims 25, 37 and 38 under 35 U.S.C. § 103(a) with the examiner relying upon Markussen '212 or Markussen EPO, Godeddel, Grau '684, Grau '332 and Mai as evidence of obviousness,

Claims 22, 23, 40 and 41 under 35 U.S.C. § 103(a) with the examiner relying upon Markussen '212 or Markussen EPO, Godeddel, Grau '684 and Grau '332 as evidence of obviousness,

Claims 26, 27, 31 and 32 under 35 U.S.C. § 103(a) with the examiner relying upon Markussen '212 or Markussen EPO, Godeddel, Mai, Grau '684 and Grau '332 as evidence of obviousness, and

Claims 39 and 42 under 35 U. S. C. § 103(a) with the examiner relying upon Markussen '212 or Markussen EPO, Grau '684 and Grau '332 as evidence of obviousness.

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[2] While this reference is not listed at page 3 of the Examiner's Answer as being relied upon, it is in fact used as evidence of obviousness in rejecting the claims in the Examiner's Answer as it was in the final rejection. We view the examiner's failure to list this reference as an inadvertent oversight.

We reverse. In addition, we raise other issues for the examiner and appellants to consider.

DISCUSSION

The formation of human insulin is described in Thim at page 2, lines 5-21 as follows:

> Human insulin consists of two peptide chains, the A-chain containing 21 amino acid residues and the B-chain containing 30 amino acid residues. The A- and B-chain are joined together by two disulfide bridges connecting the cysteinyl residue at A7 to B7 and A20 to B19, respectively. A third disulphide bridge is formed between the cysteinyl residues A6 and A11.
>
> Human insulin is produced in vivo in the pancreas in the form of preproinsulin. Preproinsulin consists of a prepeptide of 24 amino acid residues followed by proinsulin containing 86 amino acid residues in the configuration: prepeptide-B-Arg-Arg-C-Lys-Arg-A in which C is the C-peptide of 31 amino acid residues.
>
> During excretion from the islet cells the prepeptide is cleaved off and proinsulin then folds to a structure in which disulfide bridges are formed. The C-peptide is then excised proteolytically to give mature human insulin.

The compound set forth in claim 33 on appeal is termed a "mini-proinsulin" by appellants and is stated to be useful in preparing human insulin Arg^{B31} –OH (mono-Arg insulin). Specification, page 1. This compound is also described in Grau '332. Id. Further, the compound of claim 33 is stated to show insulin activity itself. Id. As seen from claim 42 reproduced above, mono-Arg insulin can be prepared by simply treating the compound of claim 33 with trypsin.[3]

Key in deciding the issues raised in all of the obviousness rejections before us for review is determining whether the compound of claim 33 is novel and unobvious. If the compound of claim 33 is novel and unobvious, all of the obviousness rejections fall

[3] This again assumes the reference in claim 42(a) to A(1-31) is a typo.

since the method claims on appeal require the use of this compound. Also, nucleic acid sequence claim 34, vector claim 35, host cell claim 36 and fusion protein claim 37, would also be patentable if the compound of claim 33 is determined to be novel and unobvious.

The examiner has relied upon Markussen '212 and Markussen EPO in the alternative in stating the rejection of claim 33. The two Markussen patent documents appear to be equivalent, or at the least, the examiner has not pointed to any significant difference in their disclosures. As such, we shall limit our consideration of the issues raised in this appeal to Markussen '212. In similar fashion, the examiner has not distinguished in any meaningful sense between Grau '684 and Grau '332. Thus, we shall limit our consideration of patentability of claim 33 in light of Grau '332.

As we understand the examiner's position in regard to the patentability of the compound of claim 33 it is as follows. Markussen '212 describes a genus of mini-proinsulin precursors at column 2, line 63-column 3, line 18 as follows:

> According to a first aspect of the present invention there is provided a DNA-sequence encoding insulin precursors of the formula
>
> $B(1\text{-}29)\text{-}(X_n\text{-}y)_m\text{-}A(1\text{-}21)$ I
>
> wherein X_n is a peptide chain with n amino acid residues, Y is Lys or Arg, n is an integer from 0 to 33, m is 0 or 1, B(1-29) is a shortened B-chain of human insulin from Phe^{B1} to Lys^{B29} and A(1-21) is the A chain of human insulin, with the proviso that the peptide chain $-X_n\text{-}Y-$ does not contain two adjacent basic amino acid residues (i.e., Lys and Arg).
>
> Preferred insulin precursors of the above formula I are B(1-29)-A(1-21), i.e. m=0 in formula I, and compounds with a relative short bridging chain between the B(1-29)- and the A(1-21)-chain.
>
> When m=1, then n is preferably 1-33, more preferably 1-15, 1-8 or 1-5 and most preferably 1-3 or 1-2. X may preferably be selected from the group consisting of Ala, Ser and Thr, the individual X's being equal or different. Examples of such preferred compounds are B(1-29)-Ser-Lys-A(1-21) and B(1-29)-Ala-Ala-Lys-A(1-21).

The examiner points out at page 5 of the Examiner's Answer[4] that the generic structural formula of the insulin precursors does encompass the compound of claim 33 if X is Thr, n is 1 and Y is Arg.

While not explicitly stated in the Examiner's Answer, we believe the examiner was aware of cases such as In re Baird, 348 F.2d 974, 29 USPQ2d 1550 (Fed. Cir. 1994) and In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992) that stand for the proposition that disclosure of a chemical genus does not necessarily render obvious any species that happens to fall within that genus. Thus, the examiner articulates a so-called motivation why one of ordinary skill in the art would select the compound of claim 33 from the genus of proinsulin compounds described in Markussen '212.

The examiner's motivation to do so involves the description in Grau '332 that "the derivative insulin-Arg^{B31}-OH in crystalline form is exceptionally stable to further tryptic degradation." Grau '332, column 2, lines 10-12. We believe the examiner's position is that once one of ordinary skill in the art understands that insulin-Arg ^{B31}-OH is a desired insulin derivative, that hypothetical person would also understand from reading the generic disclosure of the proinsulin compounds described in Markussen '212 that the species of that genus wherein X is Thr, n is 1 and Y is Arg may be cleaved by trypsin and thus produce the desired insulin-Arg ^{B31}-OH. In our view, the examiner's position is based upon impermissible hindsight.

We must view the applied prior art and the examiner's stated reasons for combining the references apart from appellants' disclosure of the present invention

[4] The pages of the Examiner's Answer are misnumbered. Pages 1 and 2 are correctly numbered while page 3 contains no page number and page 4 is stated to be page number 2 with that mistake continuing

since it is teachings in the references or knowledge generally available in the art that must suggest the desirability of combining the teachings in order to arrive at the claimed subject matter. Here, the examiner's reasoning is premised upon one of ordinary skill in the art reading the disclosure of the genus of proinsulin compounds in Markussen '212 throught the lens of Grau '332. However, we do not find the lens of Grau '322 to be as sharply focused as does the examiner.

The examiner has not analyzed Grau '332 in regard to the intermediates taught or suggested by the reference that would be useful in preparing the final products of the reference such as insulin-Arg^{B31}-OH. If the selection of the compound of claim 33 to use as the intermediate in preparing insulin-Arg^{B31}-OH would have been obvious, it seems that it would have been obvious from a consideration of Grau '322 alone on the basis of working backwards from a given desired end product and preparing a list of intermediate insulin derivatives which would result in the desired end product after tryptic digestion. For example, Example 2 of Grau '322 uses monkey preproinsulin to form insulin-Arg^{B31}-OH. It is unclear how large the list of possible intermediates is, as the examiner's analysis did not follow this path. It may be that, viewed in this light, the list of possible insulin intermediates that are capable of forming insulin-Arg^{B31}-OH by way of tryptic digestion is quite large. If so, one is put in the same position as one is in viewing the large genus of insulin compounds described by Markussen '322. Instead of analyzing Grau '322 in this light, the examiner's analysis jumps immediately to apparently the only species of the possible millions of compounds generically described

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on throughout the remainder of the document. References to page numbers of the Examiner's Answer are based upon the actual page numbers of the record document.

in Markussen '212 as the intermediate to use in Grau '322 to form insulin-Arg^{B31}-OH. We think the examiner's leap from Grau '332 to Markussen '212 was guided by appellants' disclosure of the present invention instead of the references themselves. The examiner's analysis bespeaks more of an impermissible hindsight analysis instead of a reasoned explanation of why the applied art suggests the compound of claim 33. Thus, we do not find that the examiner has properly established a prima facie case of obviousness.

As set forth above, this finding mandates reversal of all obviousness rejections set forth in the Examiner's Answer.

OTHER ISSUES

Viewing the disclosure of Markussen '212 while focused solely on the subject matter of claim 33 on appeal, we believe Markussen '212 is more relevant in determining the patentability of the compound of claim 33 than either the examiner or appellants have recognized on this record.

Markussen '212 does describe a genus of insulin precursors at column 2, line 63-column 3, line17, which encompasses a large number of compounds. As indicated above, Jones and Baird stand for the proposition that a broad chemical genus such as that described in Markussen '212 does not necessarily render obvious any specific species encompassed therein. However, that is not the end of the matter. In In re Petering, 301 F.2d 676, 133 USPQ 275 (CCPA 1962) the court was confronted with a similar factual situation. The court stated that even though Petering's claimed compounds were encompassed by a broad generic prior art disclosure, the court concluded that the broad disclosure by itself described the claimed compounds within

the meaning of 35 U.S.C. § 102(b). Id., 301 F.2d at 681, 133 USPQ at 279. However, the court went on to describe what it termed "specific preferences" for the substituents of the chemical compounds described in the applied reference, Karrer. The court concluded that it was their "opinion that the pattern of Karrer's specific preferences in connection with his generic formula constitutes a description of a definite and limited class of compounds." Id. 301 F.2d at 681, 133 USPQ at 280. The court concluded:

> We think the Karrer patent, as a printed publication, describes to one skilled in this art not only the broad class but also this much more limited class within that broad class, and we think it is immaterial that Karrer did not expressly spell out the limited classes as we have done here, it is our opinion that one skilled in this art would, on reading the Karrer patent, at once envisage each member of this limited class, even though this skilled person might not at once define in his mind the formal boundaries of the class as we have done here.

Id. .

We believe the examiner and appellants need to read Markussen '212 very carefully in light of Petering. Markussen '212 states that preferred insulin precursors includes those where m=1, n is most preferably 1-3 or 1-2 and that X is preferably Ala, Ser and Thr, X being equal or different. Thus, it may be that Markussen '212 is describing a very limited subgenus of compounds as follows:

The structural formula B(1-29)-$(X_n$-$Y)_m$-A(1-21) wherein m=1, n =1 or 2, X = Ala, Ser, Thr, X being equal or different, Y = Lys or Arg defines two subgenus, i.e., B(1-29) (X_n-Lys) A(1-21) and B(1-29) (X_n-Arg)A(1-21) wherein n = 1 or 2, X = Ala, Ser, Thr with X being equal or different.

The second subgenus consists of the following compounds:

1. B(1-29)	(Ala-Arg)	A(1-21)
2. B(1-29)	(Ser-Arg)	A(1-21)
3. B(1-29)	(Thr-Arg)	A(1-21)
4. B(1-29)	(Ala-Ala-Arg)	A(1-21)
5. B(1-29)	(Ala-Ser-Arg)	A(1-21)
6. B(1-29)	(Ala-Thr-Arg)	A(1-21)
7. B(1-29)	(Ser-Ala-Arg)	A(1-21)
8. B(1-29)	(Ser-Ser-Arg)	A(1-21)
9. B(1-29)	(Ser-Thr-Arg)	A(1-21)
10. B(1-29)	(Thr-Ala-Arg)	A(1-21)
11. B(1-29)	(Thr-Ser-Arg)	A(1-21)
12. B(1-29)	(Thr-Thr-Arg)	A(1-21)

Amino acid residue 30 of the B chain of human insulin is Thr. See, e.g., Figure 1 of Thim. Thus, compound 3 enumerated in the above table is the compound required by claim 33 on appeal, i.e., B(1-30)-Arg-A(1-21).

Upon return of the application, the examiner and appellants should carefully review the disclosure of the insulin precursors described in Markussen '212 in light of the guidance provided by In re Petering. If in fact one of the preferred subgenera of Markussen '212 consists of the 12 compounds set forth in the above table which includes the compound of claim 33, it may be reasonable for the examiner to conclude

that Markussen '212 describes the compound required by claim 33 with the specificity required by 35 U.S.C. § 102, i.e., Markussen '212 anticipates claim 33.

We are aware that a substantial portion of appellants' position in regard to the examiner's rejection is premised upon the prosecution history of Markussen '212. For example, appellants argue at the Reply Brief, page 6:

> Thus. Markussen was able to overcome the prior art by arguing that the shortened B-chain was what gave his invention its novelty and superiority and argues that a B30 Threonine residue is never present in the precursor. The Office cannot now say that "X" is equivalent to the B30 Threonine. This would completely ignore all of the arguments used to overcome the prior art, thereby invalidating the Markussen patent.

These arguments are more relevant in determining the scope of the Markussen '212 claims in an inter partes enforcement action than in determining the relevance the disclosure of Markussen '212 has in determining the patentability of claims pending ex parte before the USPTO. As seen, this argument is couched in terms of the patentability of Markussen's "invention," not the claims of Markussen '212. An inventor may describe his invention in both broad and narrow terms in the specification of the application and in the course of prosecution disavow the broader invention by way of amendment or argument. The fact that a proper construction of the claims in an issued patent[5] may result in a claim scope narrower than the broader description of the invention in the specification does not mean that the broader description of the invention disappears from the patent. Rather, the broader description remains there and must be evaluated for what it means to one of ordinary skill in the art in the context of determining the patentability of claims pending in this application. We do not

understand appellants' position to be that with appropriate selection of variables, Markussen '212 does not literally describe the compound of claim 33. Rather, appellants would have the disclosure ignored or wished away by analyzing the arguments made on behalf on Markussen in procuring the patent.

If the examiner determines that Markussen '212 describes the compound of claim 33, the examiner should revisit the issue of the patentability of the method claims pending in this application. It may be that once it is determined that Markussen '212 contains a sufficiently specific description of the compound of claim 33 so as to be anticipatory, a person of skill in this art focused on that compound would understand that due to its amino acid sequence, the compound is amenable to tryptic cleavage in order to form insulin-Arg^{B31}-OH which Grau '332 describes as possessing beneficial properties.

REVERSED

William F. Smith
Administrative Patent Judge

Toni R. Scheiner
Administrative Patent Judge

Donald E. Adams
Administrative Patent Judge

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) INTERFERENCES

[5] We take no position on appellants' arguments based upon the prosecution history of Markussen '212 in regard to their accuracy or correctness.

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ELD